

## Pharmaceutical Industry Research Credit Audit Guidelines

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                    (See “Using Exhibit D”)

## Preface and Overview

**Purpose:** The intent of this document is to provide audit technique guidelines for IRS agents and managers examining the credit for increasing research activities claimed by taxpayers in the pharmaceutical industry. These audit technique guidelines also provide helpful information to industry taxpayers. This document is not legally binding and should not be relied upon as such. This document is also not designed to remove the discretion of managers and agents in varying audit techniques or procedures appropriate to any given examination. Rather, it is designed to reduce burden for all stakeholders by (1) providing an overview of the drug development process in branded pharmaceutical companies for agents, (2) identifying audit areas that have the highest probability for errors, and (3) providing guidance on the essential information agents need to make a determination as to qualified research expenditures. This audit technique guide is not intended to address all potential research credit issues (refer to the Research Credit ATG for discussion of supply, computational or allocation issues).

These guidelines are not an official pronouncement of the law or the Service's position and cannot be used, cited, or relied upon as such. Nothing in this document precludes an agent from proposing any proper adjustment, even if the adjustment arises from an activity that would not normally be audited if the guidelines in this paper were applied.

The business activities of product development for a branded pharmaceutical generally do not give rise to an issue as to whether the company is conducting qualified research, but rather whether the expenses qualify for the research credit. An understanding of the product development phase, basic auditing techniques, and an analysis of the risks in various stages, departments, and cost centers can minimize audit burden. Upfront discussion of the audit plan with the taxpayer is critical in starting the audit. Following the steps contained herein could lead an agent to quick and sound auditing conclusions. For example, the determination of qualified research activities in the Biology department is a low audit risk. In most cases, the Biology department performs qualified research activities. Further analysis will quickly establish whether costs incurred by that department contain high-risk audit items, such as inclusion of wages for employees above first-line supervision.

**Pharmaceutical Development Process Overview:** The pharmaceutical product development process is composed of four (4) stages:

1. Preclinical/Discovery Research – where new compounds are discovered.
2. Clinical Development – conducted in three (3) phases.

Phase I – first trials in humans that test a compound for safety, tolerance and pharmacokinetics. The trials usually employ normal, healthy volunteers.

Phase II – pilot studies to determine efficacy and safety in selected populations of patients with the disease or condition to be treated, diagnosed, or

prevented. Dose and dosing regimens are assigned for magnitude and duration of effect during this phase.

Phase III – expanded clinical trials intended to gather additional evidence of effectiveness for specific indications and to better understand safety and drug-related adverse effects.

3. Regulatory Review – the New Drug Application (NDA) is submitted to a regulatory agency, such as the Food and Drug Administration, for marketing and manufacturing approval.
4. Post-Marketing – activities occurring after approval to market has been granted by the appropriate regulatory agency. These activities include Phase IV studies performed to determine the incidence of adverse reactions; to determine the long-term effect of a drug; to study a patient population not previously studied; and for marketing comparisons against other products and other uses.

Each stage of drug discovery and development may have employees engaged in qualified research. An agent should look at the function or functions of the departments and the activities of the employees, not merely the titles of the individuals and departments involved.

The department names and breakdown of duties should be viewed as an example. Individual companies may have different department names and separate functions differently from that discussed in these guidelines. It is the functions performed within a department and not the department's name that determines eligibility for the research credit.

## **Summary of Recommended Audit Procedures**

The initial requirement of the audit is a reconciliation of the expenses claimed to objective financial accounting records of the taxpayer. Depending on the company's method of operation, the amount of detailed information required could include a cost center application of expenses or a departmental/divisional analysis. In addition, the expenses may be provided on a subsidiary basis or a consolidated basis. Where a company has undergone a merger, consolidation, combination, or disposition, the agent must insure the gross receipts and qualified research expenses included in the credit computation reflect these changes in operations.

To assist in determining appropriate areas for audit, a Research Credit Wage Issue Chart and a department rating of "**low to high risk**" has been provided. The Research Credit Wage Issue Chart is attached as Exhibit D. This Chart provides guidance on the areas of most concern in each department. The "**low to high risk**" rating pertains to whether the activities performed by that department are likely to be qualified research, pursuant to IRC § 41. For purposes of this audit technique guide, risk is defined as follows:

- Low risk means it is likely that the activities are qualified research or qualified services. However, there may be other substantive issues to consider, such as whether the wage computation includes wages attributable to managers that are not engaged in the immediate supervision of qualified research.
- Medium risk means it is likely that the activities of the department include some activities that may be qualified research or qualified services. Therefore an allocation of qualified research expense activities from nonqualified research expense activities within the department is critical.
- High risk means it is unlikely that the activities performed in this department are qualified research or qualified services, as defined in IRC § 41.

If, after consideration of the above items, a decision is made to examine the issue, we recommend that the audit teams consider using the risk analysis approach in this guideline to allocate audit resources. The following recommendations summarize the audit guidelines addressed later in this document.

Stage one – Preclinical/Discovery Research. Generally, preclinical/discovery research is conducted in the biology, chemistry, pharmacology, toxicology, and drug metabolism departments of a pharmaceutical company. On occasion, portions of this work could be outsourced. During this stage of the pharmaceutical product development process, the predominant portion of the qualified research expenses should be wages paid or incurred to employees for qualified services performed by these employees. Because the research scientists in these departments are likely to be engaged in qualified activities, the activities performed in this stage have a high potential for meeting the requirements of qualified research and are classified in this audit guideline as “**low risk**”. This “**low risk**” rating does not preclude review of preclinical department expenses outside the laboratory setting.

Stage two – Clinical Development. Clinical development of a product is done in three phases. The pharmaceutical or biotechnology company may outsource much of the work to clinical research organizations (CROs). Sampling these contracts, to insure all work is performed in the United States and to review the payment terms, is recommended. The activities or departments involved in this stage will be detailed later in this document. The internal expenses of a company during this stage will have “**low**” to “**high**” audit risk depending on the type of activity performed.

Stage three – Regulatory Review. Regulatory submissions, such as the NDA, are prepared during this stage. Pharmaceutical companies have significant contact with the FDA regarding their submissions and the various aspects of getting the marketing approvals. The relevant activity or department involved in this stage is Regulatory Affairs. These activities are “**high risk**” in that it is questionable whether the work performed is qualified research as defined in IRC § 41.

Stage four – Post-Marketing. Post-Marketing activities occur after the pharmaceutical company receives marketing approval from the FDA. Much of what is done during this stage is to delineate a drug’s risks, benefits, optimal use, and marketing activities. The studies conducted often compare one drug to another drug in order to support marketing claims, such as longer lasting, faster acting, etc. The activities or departments involved in this stage include Medical Affairs/Services and

Drug Surveillance. The activities performed by employees in these departments are “**high risk**” in that it is questionable whether the work performed is qualified research as defined in IRC § 41.

## Overview of IRC Sections 174 and 41

I.R.C. § 174 generally provides that a taxpayer may treat research or experimental expenditures which are paid or incurred by him during the taxable year in connection with the taxpayer’s trade or business as expenses which are not chargeable to a capital account. The expenditures so treated are allowed as a deduction. Treas. Reg. § 1.174-2(a) provides that the term “research or experimental expenditures” as used in § 174 means expenditures incurred in connection with the taxpayer’s trade or business which represent research and development costs in the experimental or laboratory sense. The term generally includes the costs of obtaining a patent, such as attorneys’ fees expended in making and perfecting a patent application. The term research or experimental expenditures does not include expenditures for:

- Ordinary testing or inspection of materials or products for quality control
- Efficiency surveys
- Management studies
- Consumer surveys
- Advertising or promotions
- The acquisition of another’s patent, model, production or process, or
- Research in connection with literary, historical or similar projects.

Testing or inspection to determine whether particular units of materials or products conform to specified parameters is quality control testing.

I.R.C. § 41 provides a credit against tax for increasing research activities. Generally, the credit is an incremental credit equal to the sum of (1) 20 percent of the excess of the taxpayer’s qualified research expenses over its base amount, and (2) 20 percent of the taxpayer’s basic research payments determined under I.R.C. § 41(e)(1)(A). I.R.C. § 41(b) provides that the term “qualified research expenses” means the sum of the following amounts paid or incurred by the taxpayer during the taxable year in carrying on any trade or business of the taxpayer: (a) in-house research expenses, and (b) contract research expenses.

I.R.C. § 41(b) (2) defines the term “in-house research expenses” as any wages paid or incurred to an employee for qualified services performed by such employee, any amounts paid or incurred for supplies used in the conduct of qualified research, and, under regulations prescribed by the Secretary, any amount paid or incurred to another person for the right to use computers in the conduct of qualified research. However, amounts paid or incurred to another person for the right to use computers in the conduct of qualified research are not in-house research expenses to the extent that the taxpayer receives or accrues any amount from any other person for the right to use substantially identical personal property.

I.R.C. § 41(b)(2)(B) provides that the term “qualified services” means services consisting of engaging in qualified research, or engaging in the direct supervision or direct support of research activities that constitute qualified research.

Treas. Reg. §1.41-2(c) (1) provides that the term “engaging in qualified research” as used in I.R.C. § 41(b) (2) (B) means the actual conduct of qualified research (as in the case of a scientist conducting laboratory experiments).

Treas. Reg. §1.41-2(c) (2) provides that the term “direct supervision” as used in I.R.C. § 41(b) (2) (B) means the immediate supervision (first-line management) of qualified research (as in the case of a research scientist who directly supervises laboratory experiments, but who may not actually perform experiments). “Direct supervision” does not include supervision by a higher-level manager to whom first-line managers report, even if that manager is a qualified research scientist.

Treas. Reg. §1.41-2(c)(3) provides that the term “direct support” as used in I.R.C. § 41(b)(2)(B) means services in the direct support of either persons engaging in the actual conduct of qualified research, or persons who are directly supervising persons engaging in the actual conduct of qualified research. For example, direct support of research includes the services of a secretary for typing reports describing laboratory results derived from qualified research, of a laboratory worker for cleaning equipment used in qualified research, of a clerk for compiling research data, and of a machinist for machining a part of an experimental model used in qualified research. Direct support of research activities does not include general administrative services, or other services only indirectly of benefit to research activities. For example, services of payroll personnel in preparing salary checks of laboratory scientists, of an accountant for accounting for research expenses, of a janitor for general cleaning of a research laboratory, or of officers engaged in supervising financial or personnel matters do not qualify as direct support of research. This is true whether general administrative personnel are part of the research department or in a separate department. Direct support does not include supervision. Supervisory services constitute “qualified services” only to the extent provided in Treas. Reg. § 1.41-2(c) (2).

Treas. Reg. § 1.41-2(d) provides that wages paid to or incurred for an employee constitute in-house research expenses only to the extent the wages were paid or incurred for qualified services performed by the employee. If an employee has performed both qualified services and nonqualified services, only the amount of wages allocated to the performance of qualified services constitutes an in-house research expense. In the absence of another method of allocation that the taxpayer can demonstrate to be more appropriate, the amount of in-house research expense shall be determined by multiplying the total amount of wages paid to or incurred for the employee during the taxable year by the ratio of the total time actually spent by the employee in the performance of qualified services for the taxpayer to the total time spent by the employee in the performance of all services for the taxpayer during the taxable year.

If, however, substantially all of the services performed by an employee for the taxpayer during the taxable year consist of services meeting the requirements of I.R.C. § 41(b)(2)(B)(i) or (ii), then the term “qualified services” means all of the services performed by the employee for the taxpayer during the taxable year. Services meeting the requirements of I.R.C. § 41(b)(2)(B)(i) or (ii) constitute substantially all of the services performed by the employee during a taxable year only if the wages allocated (on the basis used for purposes of paragraph (d)(1) of this section) to services meeting the

requirements of I.R.C. § 41 (b)(2)(B)(i) or (ii) constitute at least 80 percent of the wages paid to or incurred by the taxpayer for the employee during the taxable year.

I.R.C. § 41(b)(2)(C) defines the term “supplies” as any tangible property other than land or improvements to land, and property of a character subject to the allowance for depreciation. In addition, Treas. Reg. § 1.41-2(b)(1) provides that supplies and personal property (except to the extent provided in Treas. Reg. § 1.41-2(b)(4)) are used in the conduct of qualified research if they are used in the performance of qualified services (as defined in I.R.C. § 41(b)(2)(B), but without regard to the last sentence thereof) by an employee of the taxpayer (or by a person acting in a capacity similar to that of an employee of the taxpayer; see example (6) of Treas. Reg. § 1.41-2(e)(5)). Finally, expenditures for supplies or for the use of personal property that are indirect research expenditures or general and administrative expenses do not qualify as in-house research expenses.

I.R.C. § 41(b)(3)(A) defines the term “contract research expenses” as 65 percent of any amount paid or incurred by the taxpayer to another person (other than an employee of the taxpayer) for qualified research. For taxable years beginning after June 30, 1996, 75 percent of any amount paid or incurred by the taxpayer to a qualified research consortium for qualified research is a qualified research expense. I.R.C. § 41(b) (3) (C).

I.R.C. § 41(d)(1) defines the term “qualified research” as research (A) with respect to which expenditures may be treated as expenses under section 174, (B) which is undertaken for the purpose of discovering information:

- (i) which is technological in nature, and
- (ii) the application of which is intended to be useful in the development of a new or improved business component of the taxpayer, and

(C) substantially all of the activities of which constitute elements of a process of experimentation, for a purpose described in IRC § 41(d) (3).

The term “qualified research” does not include any activity described in IRC § 41(d) (4).

I.R.C. § 41 (d)(3) provides that research shall be treated as conducted for a purpose described in this paragraph if it relates to a new or improved function, performance, or reliability or quality.<sup>1</sup> Research shall in no event be regarded as conducted for a purpose described in this paragraph if it relates to style, taste, cosmetic, or seasonal design factors.

I.R.C. § 41(d) (4) provides that the term “qualified research” shall not include:

- Research after commercial production
- Adaptation of existing business components
- Duplication of existing business components
- Surveys, studies, etc.
- Internal Use computer software
- Foreign research
- Research in social sciences, arts, or humanities; or

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<sup>1</sup> See generally Treas. Reg. 1.41-4(c)(2)(iv) with respect to the establishment of new functional uses, etc.

- Funded research.

In the pharmaceutical area, expenditures for quality control, ordinary testing or inspection of materials or products for quality control should not be included in either the § 174 deduction or the § 41 credit computation. Although the costs of obtaining a patent are considered research and experimental expenditures under § 174, these costs should not be included in the § 41 credit computation because these activities do not meet the requirements of qualified research.

## **Product Development Process**

### **Stage One – Preclinical/Discovery Research**

The initial identification and analysis of a compound occurs during this stage. A compound showing potential will be tested in animals and non-human systems. The FDA has established a set of standards, called Good Laboratory Practice (GLP), for this stage of development to ensure quality of science, animal testing and the resultant data for an Investigational New Drug Application (IND) or NDA. After this stage is complete, an IND is filed to permit the compound to be tested in humans.

In pharmaceutical companies, some of the professional and managerial personnel have scientific training. Although the preclinical departments of pharmaceutical companies –biology (including bioinformatics, genomics, and bioproduct discovery), chemistry, pharmacology, toxicology, and drug metabolism – are not organized under the same structure, many of the employees in these departments are scientists. In these departments, many employees work in laboratories or conduct computer-aided research on a day-to-day basis. Much of the work that is performed in these departments is exploratory research that is likely to meet the definition of qualified research. Employees in these departments also include support staff and supervisory personnel. To the extent that the employees are engaged in qualified services, their wages are qualified research expenses eligible for the research credit computation.

As discussed previously, for purposes of the research credit computation, the term “qualified services” means services consisting of (1) engaging in qualified research, (2) engaging in the direct supervision of qualified research, (3) engaging in the direct support of qualified research, or (4) engaging in the direct support of the direct supervision of qualified research.

In determining if substantially all of the services performed by an employee for the taxpayer during the taxable year consist of engaging in qualified research, or engaging in the direct supervision or direct support of research activities that are qualified research, and thus, engaged in qualified services, the following guidelines should be considered:

First, pre-clinical research in branded pharmaceutical development may involve employees who provide others with day-to-day guidance in the laboratory. These employees may be performing qualified research rather than the immediate supervision of qualified research. Based on our audit experience, an employee who is responsible for mentoring, or guiding, the

research of others in the laboratory should not be regarded as the person performing direct supervision of the qualified research, but rather as the person actually engaged in qualified research.

Second, direct supervision of qualified research is defined by activities, not by job title.

Finally, based on our experience in auditing the qualified services of the preclinical research departments of branded pharmaceutical companies, the first person outside of the day-to-day research laboratory activity spends substantially all of his or her time engaged in qualified services. (See Exhibit B and the discussion that follows).

With respect to the points above, the agent should note that some personnel may be assigned to a preclinical department on an intermittent basis. To the extent that an employee is engaged in qualified services on an intermittent basis, the portion of the employee's wages allocable to qualified services may be included in the research credit computation, based on an appropriate allocation method. See Treas. Reg. §1.41-2(d) (1).

Exhibit B is an organization chart for a preclinical department of a hypothetical pharmaceutical company. Exhibit B shows the hierarchy of a typical pharmaceutical company and the variety of titles that may be used from company to company. In this particular company, it could be determined that the senior scientist provides day-to-day guidance to the scientists and associate scientists. The senior scientist also performs laboratory research and reports to the section head (of Box B). The section head is outside the day-to-day research laboratory and performs duties that are predominantly supervisory in nature. The section head reports to one of the employees in Box C.

The activities of the employees in Box A and Box B (of Exhibit B) normally spend eighty percent or more of their time engaged in (1) the actual conduct of qualified services or (2) the direct supervision of the actual conduct of qualified research and their wages will probably qualify for the credit. In addition, these employees will probably have offices and/or workstations that are located in or in close proximity to the research laboratories. Employee job descriptions and grade levels may prove useful in identifying and grouping the employees. Conversely, wages paid to employees identified in Boxes C and D would be subject to a more detailed evaluation of their activities and should be scrutinized if their wages are included in the credit. This approach seeks to narrow the pool of employee wages by eliminating those employees that, in all likelihood, qualify for the credit, and focusing the audit on those employee wages that may not qualify. Agents should always use the appropriate risk analysis techniques to examine research credit issues.

Other records and information that may assist the agent in making these determinations may include:

- The tax workpapers used to compute the credit.
- An organizational chart of the research department.
- A list of the R&D job titles, job descriptions, and grade levels.
- A tour of the research facility.
- A physical layout of the various research departments and a listing or description of the types of researchers located in each lab (e.g., Section Head, Senior Scientist, Scientist, Associate Scientist, Lab Assistant, etc.).

It is important to note however, that e-technology may diminish the value of tours and studies of the physical layout of the department over time. Agents must evaluate the continuing utility of such techniques in light of changing practices.

For employees above first-line supervision, any salary or wage amount that is included by the taxpayer as a qualified wage should be subject to a more detailed evaluation of relevant additional records that may support the claimed expenditures. Such records could include one or more of the following:

- Business calendars.
- Travel records.
- Project reports.
- Laboratory books.
- Budgets or budget responsibility.
- Interview of the employee.

In connection with the examination of laboratory books and project reports, agents should bear in mind that a company may have concerns about their intellectual property. In such a circumstance, the agent should explain the protections afforded such intellectual property under IRC § 6103. If the taxpayer continues to express concern, the matter should be discussed with LMSB management.

The agent should consider using functional analysis and sampling techniques, depending on the size of the population. Further, the examination of these activities should be performed within the context of a risk analysis evaluation. For additional documentation guidance, refer to Exhibit A.

Some pharmaceutical companies may use a project (or matrix) approach and assign preclinical department employees to a project team that includes employees from other departments. Although employees in a preclinical department are assigned to a project team, their activities do not appear to change. Exhibit C illustrates the project structure and correlates the preclinical department employees to the department structure.

### **Preclinical Departments**

In the pharmaceutical industry the research and development process is a massive ongoing effort, which requires proper planning, timing, and teamwork. Each of the departments within an R&D organization is involved in the process and is dependent on one another. No individual department could manage the process alone. This interdependency is necessary in order to bring compounds to market that provide an improvement over existing therapies in the shortest time period possible. The following paragraphs generally describe the various areas that compose a typical preclinical department; however, it must be noted that each company has a unique structure and any current structure is subject to change.

We believe the activities of the following five departments, that make up a typical preclinical or stage one structure, have a “**low risk**” factor in satisfying the definition of qualified research. The department names are given as an example. These guidelines may be applied to the functional equivalent of the department in your company.

### **Biology**

This area is the starting point for discovery. Scientists in this department are responsible for the identification of molecular “targets” that play a key role in a particular disease process. By altering the target in some way (e.g. through drug treatment) scientists attempt to prevent, cure, delay progression, restore function or improve the condition of humans suffering from a disease or illness.

### **Chemistry**

Scientists in this department are responsible for the identification of potential drug candidates for research. They design the molecule and synthesize the actual compounds to be tested. Compounds are screened to identify those that indeed act on the target with potential therapeutic application. Scientists may modify the structure of promising compounds using a variety of chemistry techniques, thus creating molecules that are more potent and specific in their effect. Based on this research, a lead compound or class of compounds is identified for further testing and evaluation in animal models of the disease.

### **Pharmacology and Toxicology**

After the compound has been designed, the next step in discovery research is testing in tissues or animals. The Pharmacology and Toxicology Department is responsible for establishing the effects and mechanisms of action of drug candidates in laboratory animals. They will also establish the drug’s preliminary acute safety prior to moving from research into preclinical development. The pharmacology effort may be contained in the biology organization.

### **Drug Metabolism**

This department is responsible for determining the drug candidate’s absorption when administered to animals, metabolic rate and elimination process. These evaluations begin during the preclinical phase and this information is essential for the safe administration of investigational drugs to humans during the next phase of drug development. This department may also be linked to the toxicology organization.

### **Protein Discovery**

Scientists in this department look for naturally occurring proteins, antibodies and antisense that can be optimized by laboratory technicians as potential therapeutic agents.

### **Stage Two - Clinical Development**

This stage is normally conducted in three phases. In phase I, the first trials in humans are conducted for safety, tolerance, and pharmacokinetics. In phase II, testing is done to evaluate effectiveness, dosage and safety in selected populations of patients with the disease or condition to be treated or diagnosed or prevented. In phase III, expanded clinical trials are conducted to gather additional

evidence to verify dosage and effectiveness for specific indications, and to better understand safety and adverse effects.

Phase III trials are large-scale trials typically involving thousands of patients to prove effectiveness against a specific disease or condition. The FDA has established minimum standards for clinical trials involving human subjects through “good clinical practices” (GCP).

Typically, the pharmaceutical company departments involved in this stage of the drug development process are pharmaceutical development, analytical chemistry, biostatistics, pharmaceutical technology development, drug safety, toxicology, and clinical research and development.

There are generally four categories of employees in these departments. Employees are involved in the: 1) actual conduct of qualified research, 2) direct support of qualified research, 3) direct supervision of qualified research, and 4) non-qualified activities.

Direct support eligible for the credit computation consists of activities directly supporting the actual conduct of qualified research or the direct supervision of the actual conduct of qualified research. Examples of direct support of the qualified research include the machinist in machining a part of an experimental model, a secretary typing reports describing laboratory research, or a laboratory worker cleaning research equipment.

No overhead, general or administrative services or other services that only indirectly support the qualified research are qualified services.

### **Clinical Departments**

For audit purposes, pharmaceutical development, analytical chemistry, and biostatistics are considered “low risk” activities regarding the product development activities. The clinical research and development, pharmaceutical technology, and drug safety departments include both “medium risk” and “high risk” activities.

Activities to develop the process for manufacturing and quality control should be evaluated separately. The manufacturing activities include, but are not limited to, scale-up of production of bulk chemical and finished dosage forms from small research quantities to large quantities; production facility design, development and construction; and the quality control procedures required to maintain the safety and efficacy of the product for the duration of its shelf life.

### **Pharmaceutical Development**

The pharmaceutical development function develops formulations to be administered to animals during the preclinical phase, to humans during the clinical development phase, and finally to be transferred to the commercial production facilities. The responsibilities of the pharmaceutical development function include the packaging, labeling, assembly, and shipping of the clinical drugs to investigator sites to be used in clinical trials. The activities of the department include some activities that may be qualified research, and other activities that may not be qualified research. To the extent that these activities occur in stage 1 and stage 2, and relate to preclinical research or clinical testing, these are low risk activities. Activities that are not related to preclinical research or clinical testing are high risk.

### **Analytical Chemistry**

The responsibility of this department includes developing the analytical methods that are used to assure the product's drug content and purity, stability testing of the formulations to establish their shelf life and storage conditions, set product specifications, develop appropriate dosage forms (tablet, injection, etc.), developing processes of successively larger scale to support clinical development, initial safety, absorption, distribution, metabolism and excretion of the drug candidate following administration to humans during clinical development. The activities of this department are considered low risk.

### **Biostatistics**

Biostatistics is responsible for the compilation, quality control and analysis of all data collected during clinical development. This information becomes the basis of demonstrating the safety and efficacy of a drug product when administered to humans to treat specific disease states. This information is required for submission of the NDA to the FDA. Biostatistics also provides consultation to the clinical research staff in the design of the clinical studies. These activities are low risk.

### **Pharmaceutical Technology Development**

This pharmaceutical technology development function is responsible for interacting with in-house or contract research organizations in product transfer/scale-up activities necessary to support all FDA submissions. These activities include manufacture of clinical supplies at the plant site, performing stability studies, writing a section of the NDA, scale-up, or production implementation. This department also evaluates and implements new process technologies to improve production efficiencies and quality. The activities of the department include some activities that may be qualified research, and other activities that may not be qualified research. To the extent that these activities involve the manufacture of clinical supplies to be used in stage 1 or stage 2 research, they are medium risk activities.

### **Drug Safety Assessment**

This department provides toxicological support to research and development by determining the animal safety of drug candidates during all phases of research and development. Toxicology and safety testing is conducted in animals and in cell cultures to determine the relative toxicology of the compound to living systems. The majority of Drug Safety Assessment's work is involved in the completion of toxicology studies prior to use of the compound in humans. The results are used in the submission of IND's and NDA's as well as any additional studies that may be required by the FDA as a condition of NDA approval. This department's activities in the discovery and early development phases may be qualified research, and are considered medium risk. However, activities such as monitoring, and those occurring in late development (phase III) and post-marketing, are likely to be high risk.

### **Clinical Research and Development**

This department is responsible for the design, implementation, and conduct of clinical development and trial programs (Phase I, II, III and IV). Clinical investigators from outside the company usually perform these clinical trials. The company pays these investigators to perform these services. This department is also responsible for the evaluation of the data collected from the clinical trials and interpreting the safety and efficacy of the drug when administered to humans.

This department is also responsible for conducting and reporting clinical studies to obtain additional indications, uses, characteristics, combinations, dosages, or delivery forms for products. These studies can be conducted before or after the approval of an initial product. These studies are a regulatory requirement for expanding the approved indications, uses, characteristics, combinations, dosages or delivery forms of products. Many of the employees in this department are statisticians, programmers, and data managers.

The activities related to late stage product development, such as Phase IIIB or IV, research analysis may be considered in support of marketing related activities. Therefore, this department is considered medium risk because the early product development analysis may be in direct support of qualified research and the late product development analysis is not in direct support of qualified research but for marketing or regulatory purposes.<sup>2</sup> It may be difficult to segregate the activities to the appropriate phase. The audit analysis necessary here is not whether the clinical studies occur before or after the FDA approval process, but whether the clinical study meets the definition of qualified research.

### **Stage Three – Regulatory Review**

#### **Regulatory Affairs**

Regulatory Affairs consults with the development departments to assure that each drug development project contains the appropriate experiments and is conducted to standards that will support an NDA submission to the FDA. This department is the liaison between the regulatory authorities and the taxpayer. It also interacts with the FDA after the drug is approved regarding required Post-Marketing submissions. This group may also perform adverse event reporting to the FDA.

Because it is unlikely that the activities of this department are qualified activities, it is considered high risk. The activities do not involve a process of experimentation; rather, the activities involve only the compilation of data for FDA submissions. This activity does not provide a scientific or technological contribution to the research process.

### **Stage Four - Post Marketing**

All clinical trials gather information that may be of use to a company for scientific or marketing purposes. There are different types of studies that a company will perform subsequent to the completion of their stage two pivotal studies. A pivotal study is the key clinical study required by the FDA that provides evidence of the drug product's effectiveness. During the latter part of the clinical development process, additional studies are performed. Each study has a different purpose; current practice in many companies is to perform Phase IIIb studies, also known as periapproval studies. "Periapproval" studies are a unique type of clinical trial designed to address commercialization issues just prior to, during and after clinical development has been completed.

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<sup>2</sup> But see Treas. Reg. 1.41-4(c)(2)(iv) with respect to the establishment of new functional uses, etc.

Periapproval studies differ from Phase IIIB studies, which are designed to transition clinical trial volunteers from clinical development drug products to marketplace introduction. Phase IIIB studies usually run under an IND, and most often begin shortly before regulatory submission, and are completed prior to launch. The objective is to provide treatment for patients involved in a clinical trial until the product is approved and marketed. These studies may also support marketing launch claims or develop information on use in special patient populations that may not have been well studied in the NDA.

Phase IV studies primarily focus on the marketing of the product. These studies are typically very large studies, often 10,000 patients or more. These studies may have been required by the FDA to evaluate rare or infrequent adverse events. They may also provide comparisons to a competitor's drug or other therapies. This type of comparison study will help expand the labeling for the product with claims such as "faster acting" or "longer lasting". Another purpose may be the evaluation of the drug for specialized markets, such as pediatric use.<sup>3</sup> These studies are generally considered high risk.

Some companies conduct clinical development studies for a new indication after a drug has approval for marketing from the FDA. Valid studies for new indications are typically performed under stringent clinical trial formulas using the double blind methodology. A drug that has already been shown to be safe can move to Phase II or Phase III studies for a new indication with FDA approval. Companies are constantly looking for new uses for their products and may file supplemental New Drug Applications (sNDA) for those new indications. The agent must determine if the post-approval study is for scientific or marketing purposes.

## **Departments**

### **Medical Affairs/Services**

This department may serve several functions. It is responsible for scientific information support to research and development efforts. This department maintains all scientific libraries. They conduct literature searches for the scientists and provide the literature either from their own references or by requesting them from other area libraries. Medical Services also maintains an optical disc-based record of all scientific reports generated by the company for use by the scientific staff. This system also indexes, stores and retrieves scientific data from all areas of research. This department may also include individuals with a scientific background who write manuscripts on clinical studies and provide information to the general public, physicians and the scientific community regarding the company's products.

Some of the wages of employees in this department may be in direct support of qualified research. Other non-wage expenses, such as library purchase and maintenance costs, should be evaluated under section 41(b) (2). This department is considered high risk.

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<sup>3</sup> See Treas. Reg. 1.41-4(c)(2)(iv) relating to post marketing studies.

## **Drug Surveillance**

This department is primarily responsible for monitoring serious adverse effects caused by drug products after a drug has received approval from the FDA for sale. These adverse event reports are filed with the FDA and regulatory agencies worldwide. These activities are generally considered the post-marketing counterpart to the toxicology and drug safety assessment department activities. Toxicology and drug safety assessment departments evaluate drug safety during the preclinical and clinical development stages. The typical activities of the drug surveillance department are not qualified activities; this is a high risk department.

## **Related Departments**

### **Clinical Applications**

This department, sometimes called "Health Outcomes", is responsible for pharmacoeconomic research. Pharmacoeconomic research is studies used to assess and compare the value of pharmaceutical products and services. Insurance companies, third party payers and foreign governments often use these studies in their pricing or reimbursement policies. Typically, this department interacts very closely with Clinical Research and Development to add pharmacoeconomic endpoints to clinical studies. Quality of life and cost effectiveness of drugs to treat particular illnesses are addressed. The department also designs clinical trials and does compatibility and stability research for pharmacoeconomic evaluation. The activities of this department are excluded from the definition of qualified research because these activities are research in the social sciences.

### **Marketing [Outside of R&D]**

This department conducts, among other things, marketing or post-launch studies on approved products. These studies include experience trials or surveys using market research protocols and data gathering techniques, which are significantly different from the generally accepted standards of good clinical practice used in the research and development departments. The results of these marketing studies are used to more specifically highlight the advantages of a new drug or even as an introduction to physicians to more fully familiarize them with a new drug. Qualified research expenditures do not include expenditures for consumer surveys, advertising or promotion. The typical activities of this department are not qualified research activities.

### **Computer Support**

The research effort relies on state-of-the-art computer equipment. This department is responsible for the acquisition, installation, validation and operation of the computer hardware and software applications, and maintaining the data integrity of research information in support of research and development. In some companies, the activities may include virtual research modeling, bioinformatics, genomics, structural-based-drug design, systems biology approaches, and microfluidics (i.e. "lab-on-a-chip"). Computers are used to assist in the design of potential drug candidates, the acquisition and storage of information derived from all the experimentation performed during research and development and the statistical analysis of that data. The management and analysis of this data is a requirement of the various regulatory agencies. In general, some of the work of this department may involve qualified activities. Therefore, agents should consider any employee

wage expenditure adequately documented by the taxpayers that is in direct support of qualified research. To the extent that this department provides support to administrative functions, such as networks, maintenance, problem-solving, or incurs costs for computers and accessories, it is not in direct support of qualified activities.

## Exhibit A – Documentation Guidelines

### Requests for Information and Documentation

It is recommended that the agent review the Research Credit ATG for additional audit techniques.

Branded pharmaceutical companies vary in the way they are organized and accumulate cost (e.g., cost center department, or project/team), but all companies regardless of their organizational structure should be able to provide certain basic information to verify the credit claimed on the tax return. Agents should always use appropriate risk analysis techniques to evaluate the credit or the selected portions of the credit. Agents should keep in mind that auditing the research credit at a branded pharmaceutical company can be a very labor-intensive issue to develop for both the IRS and the taxpayer and may involve the wages of hundreds or even thousands of researchers.

It is strongly recommended that the agent review any requested information with the taxpayer prior to issuing any IDR to insure clarity and understanding.

Types of documentation that may be helpful in examining the research credit include:

- **Tax Workpapers** – Request the tax workpapers and other documentation used to calculate the credit. This information should be requested in electronic format (e.g., database, spreadsheet, etc.) as this will expedite the review and analysis.
- **Qualified Wages** – Request a reconciled listing of all employees' wages included in the research credit. The listing should include the employee's full name, social security number, job title, grade level, and the cost center/department/project to which the employee was assigned.
- **Qualified Supplies** – Request a reconciled summary of the supplies included in the research credit. This reconciliation should identify the cost center/department/projects to which the supplies were allocable.
- **Qualified Contract Research** – Request a reconciled summary of the qualified contract research expenses included in the credit. The summary should identify the contractors, the payments to each contractor, the type of research performed, and the objective of the research.
- **Interviews** – The agent will want to consider interviewing a high level employee early in the examination of the credit to gain a basic understanding of the R&D departments, the company's career research ladder, and the reporting hierarchy of the different departments. Later in the examination, it may be necessary to interview specific researchers, especially if sampling techniques are used to evaluate and audit the credit.

- **Tour of Research Facility** – Request a tour of the various facilities and/or a physical layout of the R&D departments. This will give the agent a general understanding of where the research is being performed, who is doing the research, who is supervising the research and which researchers actually work in and around the laboratories.
- **Organizational Chart** – Request an organizational chart for the R&D departments to get an understanding of the reporting hierarchy and perhaps the career research ladder within each department.
- **Job Titles, Grade Levels and Position Descriptions** – Request a summary of the company's job titles, position descriptions, and grade levels within the R&D departments. This information is not the deciding factor in determining who is actually doing research or who is supervising the research. However, it will provide the agent with a basic understanding of how the company is organized from a managerial and reporting structure standpoint and will help eliminate those employees that, in all likelihood, qualify for the credit and focus the audit to those employees that may require further scrutiny.

## Using Exhibit D – Research Credit Wage Issue Chart

The chart is a guide for the agent auditing the research credit in the pharmaceutical industry. The chart identifies various departments involved in the discovery, development and marketing of a drug product. The list is not exhaustive, but should be used in conjunction with the description of the various departments contained in these guidelines.

### How to use the Chart

Once a determination is made to audit the research credit an agent should identify the different departments involved (reconciliation worksheet). Using the chart, identify the department and determine the audit issue for that department. Using the chart, Exhibit A, and other available records, an Information Document Request (IDR) can be prepared to focus on that issue.

Example: The Chemistry Department is being questioned. This department is in the preclinical phase of development with a low risk rating. On the attached chart, the significant issue to be resolved is the identification of the wages for employees above the first line supervision. Keep in mind that wages for employees above the first line supervision may be allocated if the employee personally engages in qualified activities.

Example: The Pharmaceutical Technology Department, in the Clinical phase, is identified as a medium audit risk. Here, the agent should determine whether the activities constitute qualified research. If the activities qualify, the agent will then have to determine whether the wages of the employees above first line supervision are included in the computation and adjust as necessary.